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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/063,530
Filing Date: May 02, 2002
Appellant(s): EATON ET AL.

AnneMArie Kaiser
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 12/29/2005 appealing from the Office action mailed 7/6/2005.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is essentially correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal in the brief is correct.

(7) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Prior Art of Record

Hu et al., Analysis of genomic and proteomic data using advanced literature mining. Journal of Proteome Research, Vol. 2, pp. 405-412 (2003).

Haynes et al., Proteome analysis: biological assay or data archive? Electrophoresis, Vol. 19(11), pp. 1862-1871 (1998).

Chen et al., Discordent protein and mRNA expression in lung adenocarcinomas. Mol. and Cell. Proteomics, Vol. 1, pp. 303-313 (2002).

Gygi et al., Correlation between protein and mRNA abundance in yeast. Mol. Cell. Biol., Vol. 19(4), pp. 1720-1730 (1999).

Bruce Alberts et al., Molecular Biology of the Cell, 3rd ed. (1994).

Bruce Alberts et al., Molecular Biology of the Cell, 4th ed. (2002).

Benjamin Lewin., Regulation of transcription. Genes VI, Chapter 29, pp. 847-848 (1997).

Zhigang et al., Prostate stem cell antigen (PSCA) expression in human prostate cancer tissues and its potential role in prostate carcinogenesis and progression of prostate cancer. World Journal of Surgical Oncology, Vol. 2(13), pp. 1-7 (2004).

Meric et al., Translation initiation in cancer: A Novel target for therapy. Cancer Therapeutics., Vol. 1, pp. 971-979 (2002).

New England Biolabs catalog. pp. 122 (2002-2003).

Levinson et al. (U. S. Patent No. 6, 414, 117).

Falb et al. (U. S. Patent No. 6,124, 433).

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections—35 U.S.C. § 101

(i). 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

(ii). Claims 1-5 are drawn to an isolated antibody, which specifically binds to the polypeptide having SEQ ID NO: 28 (PRO1180 polypeptide). The claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility. A specific and substantial utility is one that is particular to the subject matter claimed and that identifies a "real world" context of use for the claimed invention, which does not require further research.

The specification discloses the polypeptide of SEQ ID NO: 28 (or PRO1180), the nucleic acid of SEQ ID NO: 27 encoding the polypeptide, and antibodies against the polypeptide. The specification does not disclose that PRO1180 has significant structural similarity to any fully characterized protein. There is no biological activity, expression pattern, phenotype, disease or condition, ligand binding partner, or any other specific feature that is disclosed as being associated with PRO1180. Without any information as to the specific properties of PRO1180, the mere identification of such as being a membrane-bound polypeptide possessing several transmembrane domains is not sufficient to impart a well-established utility to the claimed polypeptides and antibodies against the polypeptide. The instant disclosure fails to provide any significant information or evidence on the specific biological functions or physiological significance

of PRO1180 of the present invention and fails to disclose a patentable utility for the claimed invention.

First, the invention lacks a well-established utility. A well-established utility is a specific, substantial, and creditable utility that is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material. The sequence and prior art search does not reveal that the polypeptide of SEQ ID NO: 28, the nucleic acid encoding the polypeptide or an antibody that binds to the polypeptide has any well-established biological functions or any physiological significance. No art of record discloses or suggests any property or activity for the claimed molecules such that another non-asserted utility would be well-established for the claimed invention.

Secondly, the present invention does not disclose a specific and substantial utility. Example 18, of the instant application discloses cDNA amplification of molecule (DNA56860-1510) that is more highly expressed in normal kidney or rectal tumor compared kidney tumor or normal rectum. Thus, it is asserted the PRO1180 polypeptide encoded by the mRNA is also more highly expressed in normal kidney or rectum tumor compared kidney tumor or normal rectum. The specification further asserts that the polypeptide of the present invention is useful not only as a diagnostic marker for the presence of one or more cancerous tumors, but also serves as a therapeutic target for the tumor treatment (pages 10, 39 and 93). The Examiner notes that the PCR amplification described in Example 18 merely measures the mRNA level; it does not measure the over-expression of the polypeptide of SEQ ID NO: 28. There is no sufficient information or experimental data presented on whether the polypeptide or the

antibodies directed to PRO1180 polypeptide of the present invention can serve as a reliable diagnostic marker for kidney and rectal tumor; there is no statistical analysis of the expression data. Moreover, the assay does not establish a causative link between the polypeptide (or nucleic acid) of the present invention and kidney or rectal tumor. Without such critical information, one skilled in the art would not be able to use the molecule of the present invention as a diagnostic marker or as a therapeutic target for treatment of kidney or rectal tumor without undue experimentation. Accordingly, the results obtained based upon the assay described in Example 18 only serve as the beginning point for further research on the biological functions or physiological significance of the antibody that binds to the polypeptide of SEQ ID NO: 28 or polypeptide of SEQ ID NO: 28 or the nucleic acid encoding the polypeptide, and does not provide a specific and substantial utility for the present invention.

The specification also asserts that the nucleic acid sequences of the present invention may be used in gene therapy (the middle of page 91), the polypeptide may be employed as a therapeutic agent (the middle of page 93), and that the antibodies against the polypeptide of the present invention may be used in diagnostic assays (page 112). These asserted utilities are not specific and substantial because they do not identify or reasonably confirm a "real world" context of use. The specification fails to disclose the biological functions of the claimed antibodies and any specific diseases that are associated with or can be treated with the claimed molecules. The data do not support the specification's assertion that PRO1180 polypeptides and antibodies binding to it can be used as cancer diagnostic agents. Significant further research would have

been required of the skilled artisan to reasonably confirm that PRO1180 polypeptide is more highly expressed in normal kidney or rectal tumor compared to kidney tumor or normal rectum, and the antibody binding to such can be used as a cancer diagnostic agent; and thus the asserted utility is not substantial. In the absence of information regarding whether or not PRO1180 polypeptide levels are also different between specific normal and cancerous tissues, the proposed use of the antibodies binding PRO1180 (SEQ ID NO: 28) as diagnostic markers and therapeutic targets are simply starting points for further research and investigation into potential practical uses of the polypeptides and the antibodies binding such. See Brenner v. Manson, 383 U.S. 519, 148 USPQ 689 (Sup. Ct. 1966), wherein the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an Appellant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

In summary, all the asserted uses of the claimed invention are simply starting points for further research and investigation into potential practical uses of the claimed antibodies directed to the polypeptide of PRO1180. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." Brenner v. Manson, 148 USPQ at 696.

Claim Rejections—35 U.S.C. § 112, First Paragraph, Enablement

(iii). Claims 1-5 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial

asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections—35 U.S.C. § 102 (b)

(iv) The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(v). Claims 1, 2, and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Edwards et al. (U. S Patent No. 6,222, 029, issued 4/24/01).

Appellants contend that they are entitled to an earlier priority date that is earlier than that of Edwards et al et al. based on the disclosure of SEQ ID NO: 27 and 28 and the data of Example 18 (differential tissue cDNA expression in tumor versus normal tissue), that was disclosed in PCT Application PCT/US00/23328, filed 8/24/2000 (see Brief pages 45-46). However, Appellants have not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120. Although, the previous patent application discloses the same polypeptide (SEQ ID NO: 28) sequence and polynucleotides (SEQ ID NO: 27) encoding the polypeptide as the instant specification, the disclosure is not enabling for the instant invention directed to the antibodies binding the polypeptides and because the disclosed function (differential cDNA) expression does not impart utility to the instant invention directed the antibodies binding the polypeptide for the reasons set forth below and the previous Office Actions

dated 5/19/04, 12/30/04 and 7/06/05. Therefore, the filing date of 2 May 2002 is maintained as the priority date.

SEQ ID NO: 436 described by Edwards et al has 99.3% identity over first 151 amino acids of SEQ ID NO: 28 of the instant invention (see Office Action of 5/19/04). In addition, Edwards et al. also describe monoclonal antibodies and labelled antibodies (columns 41-42 and 46-47). Therefore, claims 1, 2 and 5 directed to antibodies are anticipated by Edwards et al. (U.S. Patent No: 6,222,029).

Claim Rejections—35 U.S.C. § 103 (a)

(vi). The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

(vii). Claims 3 and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Edwards et al. (U.S. Patent No: 6,222,029) in view of Mack et al. (U.S. Patent No: 6,294,343).

SEQ ID NO: 436 described by Edwards et al has 99.3% identity over first 151 amino acids of SEQ ID NO: 28 of the instant invention (see Appendix A). In addition, Edwards et al. also describe monoclonal antibodies and labelled antibodies (columns 41-42 and 46-47). However, it does not describe antibody fragments and labelled antibodies. Mack et al. describe humanized and fragments of antibodies (column 22).

Therefore, it would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to generate antibodies as taught by Mack et al. using the polypeptide described in Edwards et al that has 99.3% identity to SEQ ID NO: 28 over the first 151 amino acids of the instant invention. The person of ordinary skill in the art would have been motivated to generate antibodies directed to the polypeptide described by Edwards et al. because this will allow the one of skilled in the art use the antibodies to purify the protein or imaging studies or for therapeutic or diagnostic purposes. There is a reasonable expectation of success because Mack et al. have used the antibodies for purification and imaging (columns 24-26). Therefore, the claims are obvious over Edwards et al. (U.S. Patent No: 6,222,029) in view of Mack et al. (U.S. Patent No: 6,294,343).

Nature of the invention and the state of the prior art. The present invention is drawn to an antibody that binds to the polypeptide of SEQ ID NO: 28, which polypeptide does not have any defined biological functions or activities. The specification merely lists (Example 18 of page 140) that the mRNA of SEQ ID NO: 21 is more highly expressed in normal kidney or rectum tumor compared to kidney tumor or normal rectum in the assay described in Example 18. There is insufficient information, as noted above in the utility rejection section, to enable the skilled artisan to use the claimed antibodies absent undue experimentation. Even if the mRNA of SEQ ID NO: 21 that encodes the polypeptide of SEQ ID NO: 28 were more highly expressed in normal kidney or rectal

tumor compared to kidney tumor or normal rectum, the polypeptide of SEQ ID NO: 28 would not necessarily be more highly expressed in normal kidney or rectum tumor tissues because there is no correlative link established between the mRNA expression and the level of the polypeptide. The prior art teaches that the multi-level control of protein synthesis and degradation in cells and tissues means that only the direct analysis of mature protein products can reveal their correct identities, their relevant state of modification and/or association and their amounts (see, e.g., Haynes et al., Electrophoresis 19: 1862-1871, 1998, bottom of left column of page 1870). Haynes et al., who studied more than 80 polypeptides relatively homogeneous in half-life and expression level, found no strong correlation between polypeptide and transcript levels. For some genes, equivalent mRNA levels translated into polypeptide abundances, which varied more than 50-fold. That is polypeptide levels cannot be accurately predicted from mRNA levels (page 1863, second paragraph and Figure 1). The literature also cautions researchers against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. Hu et al., analyzed 2286 genes that showed a greater than 1 –fold difference in mean expression level between breast cancer samples and normal samples in a microarray (see, Journal of Proteome Research 2: 405-412, 2003, middle right hand column of page 408). Hu et al. discovered that, for genes displaying a 5–fold change or less in tumors compared to normal, there was no evidence of correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression

level and a published role in the disease (see discussion section). Even if increased mRNA levels could be established for PRO1180, it does not follow that polypeptide levels would also be amplified.

Chen et al. (Molecular and Cellular Proteomics 1: 304-313, 2002) disclose that twenty-eight of the 165 protein spots (17%) or 21 of 98 genes (21.4%) had a statistically significant correlation between protein and mRNA expression (abstract). In addition, it is stated that no significant correlation between mRNA and protein expression was found (r=-0.025) if the average levels of mRNA or protein among all samples were applied across the 165 protein spots (98 genes). The reference also teaches that the mRNA/protein correlation coefficient also varied among proteins with multiple isoforms, indicating potentially separate isoform-specific mechanisms for the regulation of protein abundance. Chen et al. clearly state, "the use of mRNA expression patterns by themselves, however, is insufficient for understanding the expression of protein products" (see page 304). In a study using a quantitative analysis of mRNA and protein expression within the same lung adenocarcinomas, it was shown that only a subset of the proteins exhibited a significant correlation with mRNA abundance.

(10) Response to Argument

I. Rejection of claims 1-5 under the utility requirement of 35 USC §101

At the top of page 4 of the Brief, Appellants argue that the asserted patentable utility of PRO1180 polypeptide is based on the disclosure in Example 18 of the instant application that the mRNA encoding the PRO1180 polypeptide is more highly

expressed normal kidney or rectal tumor compared to kidney tumor or normal rectum. From the bottom of page 5 to the top of page 8 of the Brief, Appellant, citing case law and MPEP, reviews the legal standard for utility, with which the Examiner takes no issue.

Beginning at page 8 of the Brief, Appellants argue the differential expression of PRO1180 mRNA was detected using well-established technique of quantitative PCR amplification of cDNA libraries isolated from different human normal and tumor tissues samples. To ensure that equivalent amounts of nucleic acid were used in each reaction, the cDNA for β-actin was used as a control. Appellants argue that identification of the differential expression of a PRO polypeptide-encoding mRNA in one or more tumor tissues as compared to one or more normal tissues of the same tissue type "renders the molecule useful diagnostically for the determination of the presence or absence of tumor in a subject suspected of possessing a tumor." It is further asserted that because it is well established that changes in mRNA levels lead to changes in the level of the encoded protein, one would expect the PRO1180 protein to be differentially expressed in normal kidney or rectal tumor compared to kidney tumor or normal rectum. Appellants argue that anti-PRO1180 antibodies may be used in diagnostic assays for PRO1180 (polypeptide), e.g., detecting its expression (and in some cases, differential expression) in specific cells, tissues or serum. Various diagnostic assay techniques known in the art may be used, such as competitive binding assays, direct or indirect sandwich assays and immunoprecipitation assays conducted in either heterogeneous or homogeneous phases. Appellants assert that taken together, the specification clearly discloses the

"real world" use of the claimed antibodies as diagnostic tools for cancer, particularly kidney and rectal tumors.

Appellant's arguments have been fully considered, but is not deemed to be persuasive for the following reasons. An assay using PCR amplification as described in Example 18, the Appellants merely measures the mRNA level; it does not measure the over-expression of the polypeptide of SEQ ID NO: 28. There is no evidence regarding whether the level of PRO1180 polypeptide of SEQ ID NO: 28 is more highly expressed in normal kidney or rectal tumor compared to kidney tumor or normal rectum tissues. There is no sufficient information or experimental data presented on whether the polypeptide or the antibodies binding such (SEQ ID NO: 28) of the present invention can serve as a reliable diagnostic marker for kidney and rectal tumor. Moreover, the assay does not establish a causative link between the polypeptide (or antibodies) of the present invention and kidney and rectal tumor. Without such critical information, one skilled in the art would not be able to use the polypeptide of the present invention as a therapeutic target for treatment of kidney and rectal tumor without undue experimentation. The information disclosed in the instant specification is preliminary at best. Finally, art indicates that the changes in mRNA expression do not correlate with polypeptide levels (Hu et al., Haynes et al. Gygi et al. and Chen et al.). Clearly further research would be required to determine whether the PRO1180 polypeptide or antibodies binding the polypeptide can serve as a reliable diagnostic marker for kidney and rectal tumors or as a therapeutic target for treatment of kidney and rectal tumors. Accordingly the claimed utility is not substantial.

Appellants assert that to establish a *prima facie* showing that the claimed subject matter lacks utility, the Examiner must "provide evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility" (see page 9 of the brief). Appellants claim that the Examiner has issued first Office Action, final Office Action and a second final office action after RCE, during the prosecution of the instant application. In addition, it is asserted that none of these papers provide any evidence that one of ordinary skill in the art would reasonably doubt the asserted utility. However, the Examiner did provide Hu et al. and Haynes et al. and Chen et al. references in the Final Office Action dated 12/30/05 (discussed in page 4 of the Office Action) to argue that there was no significant correlation between mRNA expression and corresponding polypeptide expression. In addition, Office provided Chen et al. reference along with the Final Office action dated 7/6/05 (page 5).

In page 10 of the brief, Appellants argue that during the course of the prosecution, the Examiner had made several irrelevant arguments regarding gene amplification and an increase in gene expression, as well as the role of aneuploidy in cancer, using Sen and Pennica et al references. However, as conceded by the Appellants the Examiner did indicate in the Final Office Action mailed 7/06/2005 that Example 18 did measure mRNA levels in the tumor and normal controls. Thus, Sen and Pennica et al references were considered no longer relevant. It is also noted that the Examiner had previously incorrectly indicated that the expression was based on microarray experiments. However, Example 18 expression was based on PCR analysis of cDNA libraries.

The Appellants assert that the Examiner states that the specification discloses that the PRO1180 polynucleotide is more highly expressed in normal kidney or rectal tumor compared to kidney tumor or normal rectum tissue, and that Appellants have asserted the use of the molecule for diagnosis (page 10 of the Brief). Further it is asserted the Examiner has rejected this utility, stating that "there is no supporting evidence to indicate that the polypeptide encoded by the polynucleotide of the instant invention is also differentially expressed in the various normal and tumor tissues and as such one of skill in the art would conclude that it is not supported by a substantial asserted utility or well-established utility" (Final Office Action dated 12/30/04 at page 4).

The Examiner initially rejected this utility because of the insufficiency of data presented in Example 18. The Examiner argued that there is no supporting evidence to indicate that the polypeptide encoded by the polynucleotide of the instant invention is also differentially expressed in normal tissues compared to their tumor tissue counterparts, and as such one of skilled in the art would conclude that it is not supported by a substantial asserted utility or a well-established utility. Although, the specification claims that the polynucleotide is more highly expressed in normal kidney or rectal tumor compared to kidney tumor or normal rectum, the specification does not teach what is the normal level of expression, does not indicate how high the expression level is compared to, for example, kidney and rectal tumor; and does not provide a statistical correlation to the level of expression (for example, there is no indication of how many samples were compared to study the expression). Furthermore, even if the tumor is malignant, the specification fails to describe the type or kind of tumor present in

kidney or rectal tissue. Without knowing the identity of the kidney or rectal tumor, one of skill in art cannot use the polypeptides for diagnosis or therapeutic purposes as asserted. The specification does not disclose a correlation between any specific disorder and the altered level or form of the claimed polypeptides. Also, the specification does not predict whether the polypeptides would have high or low expression in a specific, diseased tissue (rectal tumor or kidney tumor) compared to the healthy tissue control. In addition, the specification does not teach or describe the function of this yet to be identified polypeptide (see pages 5-6 of the Examiner Action mailed 5/19/2004). Hu et al., (2003), cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue (see pages 4, 5, 13 and 16 of the Examiner Action mailed 12/30/2004).

Secondly, the Examiner argued, "polypeptide levels cannot be accurately predicted from mRNA levels" (Haynes et al. (1998), Chen et al. (2002)) and Gygi et al. (1999). See Examiner Action mailed 7/06/2005 pages 6-7, 10, 12 and 13. Thus, the Examiner concluded that "further research needs to be done to determine whether the decrease or increase in PRO1180 cDNA expression compared to normal kidney or rectal tissues supports a role for the peptide in the cancerous tissue; such a role has not been suggested by the instant disclosure" (page 5 of the Examiner Action mailed 7/06/2005). The Appellants assert that based on the above arguments, the Examiner has not established a *prima facie* case lacking utility for claims 1-5 directed to the antibodies (page 11 of the brief). Appellants also assert that with the exception of Hu et al., Haynes et al., Gygi et al., and Chen et al. references, the Examiner's assertions are

not supported by any facts, evidence or reasoning (Brief page 10). It is further argued that these references do not support the Examiner's position. Appellants thus conclude that there is simply no evidence on the record to support the Examiner's assertion that the asserted utility is not substantial, and that the invention is incomplete.

Appellants also note on page 12 of the Brief that in the closely related application Serial No. 10/063, 684, claims drawn to nucleic acids of SEQ ID NO: 27 which encodes the PRO1180 polypeptide, the Examiner has acknowledged that the nucleic acids have utility (see brief page 12). As indicated in the Office Action dated 6/14/05, page 2 in the application Serial No. 10/063, 684, the Examiner had agreed that the message difference (nucleic acids) could be used as diagnostic tool for kidney or rectal tumors. Appellants argue that, since the Examiner stated that the "differentially expressed message can be used as diagnostic tool for kidney or rectal tumors is found to be persuasive," and thus the Examiner's rejection of the exact same data in the instant case is moot in light of this statement. This argument is not found to be persuasive because although, both applications recited the same experiment (Example 18, with differences in message expression (NOT protein) in rectal or kidney tissues), claims of Serial No. 10/063, 684 were drawn to nucleic acids and thus found to have utility compared to the instant invention where claims are drawn to antibodies and do not have substantial utility because there is no nexus between the differential mRNA expression of example 18 and protein expression (PRO1180) of the instant invention.

From page 13 to 17 of the Brief, Appellants refer to the declaration of Mr. Grimaldi filed under 37 CFR 1.132 (20 August 2004) and argue against the Hu et al.

reference. Appellants quote from paragraphs 6 and 7 of the declaration stating that "semi-quantitative analysis employed to generate the data of example 18 is sufficient to determine if a gene is over or under expressed in tumor cells compared to corresponding normal tissue". Further it asserted by Mr. Grimaldi that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. Mr. Grimaldi also asserted that, if a difference is detected, this indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, i.e., to screen samples to differentiate between normal and tumor". It is further asserted that PTO's assertions are contradicted by Mr. Grimaldi's statement, "the precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue." Appellants assert that this declaration makes clear that since it is the relative level of expression between normal tissue and suspected cancerous tissue that is important, how high the level of expression is in normal tissue is irrelevant (see top of page 14). Further, Appellants argue that Mr. Grimaldi states that if a difference is detected using these techniques, "this indicates that gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes." Thus, Appellants contend that it is the uncontested opinion of an expert in the field that the results are reliable enough to indicate that the claimed antibodies are useful as diagnostic tools. This has been fully considered but is not found to be persuasive. It is also noted that the expert

has interest in the outcome of the case, since Mr. Grimaldi is listed as an inventor and is employed by the assignee.

In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, the nature of the fact sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). In the instant situation, the nature of the fact sought to be established is whether or not a approximately 2-fold amplification of the message amplification (as suggested by the declaration) encoding PRO1180 is significant. However the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, as discussed above, Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column) and discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). The specification fails

to disclose any specific "fold amplification" that is required between normal and cancerous tissue for a diagnostic determination. Is a 1-fold, a 5-fold, a 10-fold, or a 100-fold difference required? If the "fold amplification" were disclosed in the specification to be 100-fold, for example, then the cDNA that encodes the PRO1180 polypeptide would likely have a specific and substantial utility as a diagnostic marker for rectal or kidney tumors. However, such is not the case here. Most importantly, an assay using cDNA analysis as described in Example 18 merely measures the mRNA level; it does not measure the over-expression of the polypeptide of SEQ ID NO: 28 or antibodies that bind to the polypeptide of SEQ ID NO: 28.

Beginning at the 2nd paragraph of page 15 of the Brief, Appellants criticize the publication of Hu et al. and claim that Hu et al. observations are due to the "bias in the literature" toward the more prevalent ER-positive tumors as the explanation for the lack of any correlation between number of publications and gene expression levels in less-prevalent (and, therefore, less studied) ER-negative tumors, citing a statement from the article (3rd paragraph of left column of page 412) as evidence. Thus, it is the contention of the Appellants that because of this intrinsic bias, Hu's methodology is unlikely to ever note a correlation of a disease with less differentially expressed genes and their corresponding proteins, regardless of whether or not an actual relationship between the disease and less differentially expressed gene exists. Further, Appellants argue that Hu et al. do not say that a correlation in their study means that genes with less than five-fold change in level of expression in cancer cannot serve as a molecular marker of cancer. Appellants' argument has been fully considered, but is not deemed to be

persuasive for the following reasons. Hu et al. teach that their study has two implications. First, a careful hunt for corroborating evidence of a role in breast cancer should precede any further study of genes with less than 5-fold expression level change. Second, any genes with 10-fold change or more are likely to related be to breast cancer and warrant attention (2nd paragraph of left column of page 412). Hu et al. teach that it is likely that this threshold will change depending on the disease as well as the experiment (2nd paragraph of left column of page 412). Hu et al. states clearly: "It is not uncommon to see expression changes in microarray experiments as small as 2-fold reported in the literature. Even when these expression changes are statistically significant, it is not always clear if they are biologically meaningful" (bottom of right column of page 411). Hu et al. further states: "in any microarray experiment, thousands of genes may demonstrate statistically significant expression changes, but only a fraction of these may be relevant to the study" (1st paragraph of left column of page 405). In addition, Hu et al. comprehensively summarized and estimated the relative strengths of all human gene-disease relationship in Medline, and analyzed a microarray expression dataset comparing breast cancer and normal breast tissue in the context of existing knowledge (see, e.g., Abstract of Hu et al.). While it is true that "relationship established by frequency of co-citation do not necessarily represent a true biological link", as Hu et al. stated, "it is strong evidence to support a true relationship" (1st paragraph of right column of page 411). Further, while some functional molecules are not included in the analysis, a sample size of 2286 genes is sufficient to validate the author's conclusion. The purpose of a statistical analysis is to predict the property or

behavior of the overall population based upon analysis of a sample of the population. In view of the limited disclosure in the instant case, lack of disclosure of the "fold amplification" that was used to determine whether a higher expression was significant, lack of the statistical analysis, and lack of establishment of a correlative link between gene expression and protein level or a causal link between mRNA expression and melanoma tumour, the teachings of Hu et al. support the PTO's position that further research is needed to reasonably identify or confirm a specific and substantial utility for the instantly claimed polypeptide of SEQ ID NO: 28 and the antibodies binding the polypeptide.

Appellants argue that the lack of a known role for PRO1180 in cancer does not prevent its use as a diagnostic tool for cancer (see Page 16 of the Brief). Although, the utility is credible and specific it is not substantial. Appellant quotes from M.P.E.P. § 2107 regarding the requirement for a substantial asserted utility. Appellant argues that they have demonstrated at least one reasonable use for the PRO1180 polypeptide as a diagnostic marker for cancer. It is asserted that the mere identification of altered expression in tumors is relevant to diagnosis of tumors, and, therefore, provides an immediate benefit to the public. This has been fully considered but is not found to be persuasive. M.P.E.P. § 2107 I states:

> A "substantial utility" defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities.

In the instant case, the asserted utility that PRO1180 polypeptides or antibodies binding to such are useful as diagnostic markers for cancer is not substantial in that

further research is required to reasonably confirm a real world context of use. In order for PRO1180 polypeptide or the antibodies binding to be useful as a cancer diagnostic, there must be a detectable change in the amount or form of PRO1180 polypeptide between cancerous and healthy tissue. In the instant case, the evidence of record indicates that (1) cDNA is more highly expressed in normal kidney or rectal tumor compared to kidney tumor or normal rectum and (2) increased mRNA levels do not reliably correlate with increased polypeptide levels (Hu et al., Chen et al., Haynes et al. and Gygi et al). In view of this, the skilled artisan would have viewed the cDNA amplification results as preliminary with respect to the utility of the encoded polypeptides or the antibodies binding the polypeptide, and would have had to experiment further to reasonably confirm whether or not PRO1180 polypeptides or antibodies binding to the polypeptide PRO1180 (SEQ ID NO: 28) can be used as a cancer diagnostic agent.

Appellants contend that the data in Example 18 and the 1st Grimaldi declaration are therefore sufficient to establish the asserted utility, and that the Examiner has not rebutted the presumption of utility that the Appellants' application is afforded. Further Appellants contend that Mr. Grimaldi is an expert in the field who conducted or supervised the experiments at issue and his declaration is based on personal knowledge of the relevant facts at issue. This has been fully considered but is not found to be persuasive. As discussed above, in assessing the weight to be given expert testimony, the examiner may properly consider, among other things, (1) the nature of the fact sought to be established, (2) the strength of any opposing evidence, (3) the

interest of the expert in the outcome of the case, and (4) the presence or absence of factual support for the expert's opinion. (1) In the instant case, the nature of the fact sought to be established is whether or not cDNA amplification is predictive of increased protein levels. (2) It is important to note that the instant specification only discloses cDNA amplification data for PRO1180 (i.e., data regarding amplification of PRO1180 mRNA), and does not disclose any information regarding PRO1180 polypeptide levels or antibodies binding polypeptide PRO1180. Furthermore, there is strong opposing evidence showing that mRNA amplification is not predictive of protein levels in normal and cancerous tissues and, in turn, that increased mRNA levels are frequently not predictive of increased polypeptide levels. See, e.g., Hu et al., discussed *supra*. (3) Regarding the interest of the expert in the outcome of the case, it is noted that Mr. Grimaldi is named as one of the inventor and is employed by the assignee. (4) Finally, Mr. Grimaldi refers to facts; however, the data is not included in the declaration so that the examiner could not independently evaluate them. There is no protein data. In conclusion, the Examiner submits that based on consideration of the evidence as a whole, the rejection is proper.

Beginning at page 17 of the Brief, Appellants argue that the Haynes et al., Chen et al., and Gygi et al., do not refute Appellants assertion that a change in mRNA levels leads to a corresponding change in the level of the encoded protein. Contrary to Appellants assertion that Haynes et al. does not contradict the utility and enablement of the instant claims, Haynes et al. states that "These results suggest that even for a population of genes predicted to be relatively homogeneous with respect to protein half-

life and gene expression, the protein levels cannot be accurately predicted from the level of the corresponding mRNA" (page 1863, 2nd paragraph). Appellants contend that Haynes et al. did not examine whether a change in transcript level for a particular gene led to a change in the level of expression of the corresponding protein. Haynes et al., had studied more than 80 polypeptides relatively homogeneous in half-life and expression level found no strong correlation between polypeptide (steady state) and transcript levels. Appellants assert that Haynes et al. reported that they "found a general trend but no strong correlation between protein and transcript levels". However, Appellants assert that inspection of Figure 1 shows clear correlation between the mRNA levels and protein levels measured. Further it is claimed that this correlation is confirmed by an inspection of the full-length research paper from which the data in Figure 1 were derived, (Gygi et al. Molecular and Cellular Biology, 1999, 1720-1730, a reference provided by the Appellants after final). Although Appellants assert that there is a strong correlation between mRNA expression and protein expression, Gygi et al. conclude that transcript levels provide little predictive value with respect to the extent of the protein expression (page 1730, last line). Furthermore, Gygi et al. clearly state that the correlation between mRNA and protein levels was insufficient to predict protein expression levels from quantitative mRNA data (see abstract). Appellants contend that Haynes and Gygi et al. looked at the static level of mRNA across many genes not changes in the level of expression for single gene. In response to Appellants argument that the references fail to show certain features of Appellant's invention, it is noted that the features upon which Appelant relies (i.e., changes in message levels are correlated

to protein levels) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). While it is true that Haynes and Gygi references discussed the steady state levels, they were relied upon by the Examiner to illustrate the point that in general there is no correlation between mRNA expression and the polypeptide expression.

In addition, Appellants have failed to establish that there exists a correlation between the message levels and the protein levels of PRO1180 either in steady state or in a dynamic changing environment. Appellant appear to argue that Haynes teaches that there was a general trend but no strong correlation, between protein and transcript levels and there is a positive correlation between mRNA and protein among most of the 80 yeast proteins studied. On the another hand, Appellant argues that the Haynes et al. did not compare mRNA expression levels and protein levels in the same yeast cells and thus the analysis by Haynes et al. is not applicable to the present application. Appellants' argument has been fully considered, but is not deemed to be persuasive for the following reasons. First, Appellant ignores the overall teachings of Haynes et al. At 2nd paragraph of left column of page 1863, Haynes et al. clearly states, "For some genes studied, equivalent mRNA transcript level translated into protein abundances which varied by more than 50-fold. Similarly, equivalent steady state protein expression levels were maintained by transcript levels varying by as much as 40-fold". Clearly, Appellant's argument that a positive correlation exists between mRNA and protein is not true. Moreover, Haynes et al. conclude "The multi-level control of protein synthesis and

degradation in cells means that only the direct analysis of mature protein products can reveal their correct identities, their relevant state of modification and/or association and their amounts" (bottom of left column of page 1870). Accordingly, the limited disclosure in the instant case does not meet the legal standard for a specific and substantial utility. Furthermore, Appellant' arguments that Haynes et al. did not compare mRNA expression levels and protein levels in the same yeast cells are invalid because Haynes et al. clearly sates: "we have determined the correlation of expression at the mRNA and protein levels for a population of selected genes in the yeast *Saccharomyces cerevisiae* growing at mid-log phase (the 2nd paragraph of left column of page 1863).

At the middle of page 19 of the Brief, Appellants assert that Chen et al. (2002, Molecular and Cellular Proteomics 1:304-313) is not relevant to Appellant's assertion that changes in the level of mRNA lead to changes in the level of the encoded polypeptide. Further on page 19 of the Brief, Appellants argue that Chen et al. "read in its entirety" provides scant evidence to counter Appellants' asserted utility because portions of reference support Appellants' assertions, and the remaining portions provide little insight into the relationship between changes in mRNA levels and changes in the corresponding protein levels for mRNA that is differentially expressed in tumor cells relative to normal cells. Appellants' argument has been fully considered, but is not deemed to be persuasive for the following reasons. Chen et al. compared mRNA and protein expression for a cohort of genes in the same lung adenocarcinomas. Only 17% of 165 protein spots or 21% (21of 98) of the genes had a significant correlation between protein and mRNA expression levels. That is only a subset of the protein exhibited a

significant correlation with mRNA abundance. Chen et al. clearly state that "the use of mRNA expression patterns by themselves, however, is insufficient for understanding the expression of protein products" (p. 304) and "it is not possible to predict overall protein expression levels based on average mRNA abundance in lung cancer samples" (pp. 311-312). Chen et al. summarize their findings by stating, "using a quantitative analysis of mRNA and protein expression within the same lung adenocarcinomas, we showed that only a subset of the proteins exhibited a significant correlation with mRNA abundances" (abstract). Furthermore, as with the Haynes et al. reference above, Appellants are challenging portions of the reference selectively, including the assertion that the reference does not address the change in the mRNA levels and changes in protein levels, Appellants are again arguing a limitation that is not present in the claims. The Chen reference taken as a whole clearly argues against Appellants position that there is a correlation between mRNA and protein expression. Since, the instant specification does not provide additional information regarding whether or not PRO1180 polypeptide is more highly expressed in normal kidney or rectal tumor compared to kidney tumor or normal rectum, and thus the skilled artisan would need to perform additional experiments to reasonably confirm such. Therefore, the asserted utility for the claimed polypeptides or antibodies binding such is not in currently available form, the asserted utility is not substantial.

Appellants on page 22 of the Brief assert that the Examiner has failed to establish a *prima facie* case that one of skilled in the art would doubt Appellants' asserted utility. It is asserted by the Appellant that the Examiner has relied on

essentially two arguments in rejecting the pending claims for lack of utility. First, it is claimed that the examiner has questioned the sufficiency, reliability and significance of the data reported in Example 18 as well as the supporting first Grimaldi declaration. Secondly, it is asserted that the Examiner relied on the references of Haynes et al. and Gygi et al. to support the assertion that the polypeptide levels cannot be accurately predicted from mRNA levels. However, the Examiner in rejecting the pending claims for lack of utility, noted that PCR amplification as described in Example 18, merely measures the mRNA level; it does not measure the over-expression of the polypeptide of SEQ ID NO: 28. There is insufficient information or experimental data presented on whether the polypeptide or antibodies of the present invention can serve as a reliable diagnostic marker for rectal or kidney tumor and there is no statistical analysis of the expression data (mRNA). Moreover, the assay does not establish a causative link between the polypeptide of the present invention and kidney or rectal tumors. Without such critical information, one skilled in the art would not be able to use the molecule of the present invention as a diagnostic marker or as a therapeutic target for treatment of melanoma without undue experimentation. Accordingly, the results obtained based upon the assay described in Example 18 only serve as the beginning point for further research on the biological functions or physiological significance of the antibody that binds to the polypeptide of SEQ ID NO: 28 or polypeptide of SEQ ID NO: 28 or the nucleic acid encoding the polypeptide, and does not provide a specific and substantial utility for the present invention. In addition, the Examiner has cited Hu et al. that cautions researchers against drawing conclusions based on small changes in transcript

expression levels between normal and cancerous tissue. Furthermore, the Examiner has also cited Haynes et al. and Chen et al. references to teach that mRNA levels do not in general predict protein levels in general. In view of the totality of the evidence, the rejections for lack of utility and enablement are proper.

Appellants on page 23 of the Brief indicate that they have provided sufficient rebuttal evidence (including the first Grimaldi declaration) of utility and also claim that they have established that the gene encoding the PRO1180 polypeptide is differentially expressed in certain cancers (page 24 of the brief). Contrary to Appellants assertion that the Examiner has not provided any evidence or reasoning to challenge the reliability and significance of the data in Example 18 which reports that the mRNA for PRO1180 is more highly expressed in normal kidney or rectal tumor compared to kidney tumor or normal rectum respectively, the Examiner has provided published prior art that (1) cautions researchers against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue and (2) references that teach that mRNA levels do not in general predict protein levels in general. Appellants contend that Grimaldi declaration establishes that it is the opinion of an expert in the field who has personal knowledge of the facts surrounding Example 18 that there is at least a two-fold difference in mRNA for PRO1180 between the tumor tissue and the counterpart normal tissue, and that the PRO1180 genes, polypeptides and antibodies are useful for differentiating tumor tissue from normal tissue. This has been fully considered but not found to be persuasive because this appears to be declarant's opinion, and is not supported by fact or evidence (See Office Action

12/30/2004, page 7 and 11). There is no description in the specification that would indicate a correlation with higher or lower expression levels of the message to the PRO1180 polypeptide. It remains that; there is no information on the record as to whether the claimed protein is expressed at all in the rectal or kidney tissue, cancerous or otherwise. The specification does not disclose any special feature or prognosis, of rectal or kidney tumors indicating differential expression to distinguish tumor tissue from normal tissue. It is left to the skilled artisan to determine the significance (if any) of such difference. Such constitutes the type of further research required to bestow a substantial utility on the claimed invention, that of the antibodies to the PRO1180 polypeptide.

Appellants contend on page 25 of the Brief that it is well established in the art that in most cases a change in the level of mRNA for a particular protein leads to corresponding change in the level of the encoded protein. Appellants assert that the second declaration provided by Mr. Grimaldi supports this assertion. Citing paragraph 5, of the declaration Appellants contend that 'the detection of increased mRNA expression is expected to result in increased polypeptide expression, and detection of decreased mRNA expression is expected to result in decreased polypeptide expression. At paragraph 4 of the second Grimaldi declaration, the declarant discusses mutations of Her2/Neu (c-erbB2), and chromosomal translocations that are known to be associated with cancer, and states that "If the chromosomal aberration results in the aberrant expression of a mRNA and the corresponding gene product (the polypeptide) as they do in the aforementioned cases, then the gene product is a promising target for cancer therapy, for example, by the therapeutic antibody approach." This argument has been

fully considered but is not deemed persuasive because it evinces that the instant specification provides a mere invitation to experiment, and not a readily available utility. The PRO1180 gene, unlike Her2/Neu, has *not* been associated with tumor formation or the development of cancer, nor has it been shown to be predictive of such. Similarly, unlike t (5;14), no translocation of PRO1180 gene is known to occur. All that the specification demonstrates is that the PRO1180 nucleic acid was more highly expressed in normal kidney or rectal tumor compared to kidney tumor or normal rectum tissues. No mutation or translocation of PRO1180 has been associated with rectal or kidney cancer. In the absence of any of the above information, all that the specification does is present evidence that the cDNA encoding PRO1180 polypeptide is amplified in an unknown number of samples, and invite the artisan to determine the rest of the story. Such is insufficient to meet the requirements of 35 U.S.C. § 101 for the claimed antibodies binding the polypeptides.

In addition, Appellants assert that the declaration submitted by Dr. Polakis asserts that, "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein (at paragraph 6 of the declaration). Beginning at the top of page 25 of the Brief (see also pages 33-35 of the Brief), Appellant argues that it is more likely than not for increased mRNA levels to predict increased protein levels. Appellant presents a declaration by Dr. Polakis under 37 CFR 1.132 as evidence that mRNA expression correlates well with protein levels in general. In the declaration, Dr. Polakis states that a primary focus of the tumor antigen project is to identify tumor cell markers useful as targets for diagnosis and

treatment of cancer in humans. Dr. Polakis states that a variety of scientific techniques, including microarray analysis, have been used for detecting and studying differential gene expression in human tumor cells relative to normal cells at genomic DNA, mRNA, and protein levels. Dr. Polakis states that approximately 200 genes transcripts are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Dr. Polakis states that antibodies to about 30 of the tumor antigen proteins have been developed and used to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. Dr. Polakis states approximately 80% of samples show correlation between increased mRNA levels and changes in the level of protein expressed from that mRNA. Dr. Polakis states that it remains a central dogma in molecular biology that increased RNA levels are predictive of corresponding increased levels of the encoded protein. Dr. Polakis characterizes the reports of instances where such a correlation does not exist as exceptions to the rule. The declaration of Dr. Polakis is insufficient to overcome the rejection of claims 1-5 under 35 U.S.C.§101 and Appellant's argument is not deemed to be persuasive for the following reasons.

First of all, it is important to note that Dr. Polakis clearly states that a variety of scientific techniques, including microarray analysis, have been used for detecting and studying differential gene expression in human tumor cells relative to normal cells at genomic DNA, mRNA, and protein levels. Dr. Polakis does not state that tumor versus normal differential tissue expression using PCR amplification analysis alone can establish the use of a polypeptide or the antibodies as a diagnostic marker for a specific

tumor. Secondly, Dr. Polakis states approximately 80% of the samples show correlation between increased mRNA levels and changes in the level of protein expressed from that mRNA. However, Dr. Polakis does not state whether the increase in protein level was significant enough to be meaningful as being a diagnostic marker for kidney or rectal tumors. Thirdly, although, Dr. Polakis states that approximately 200 genes transcripts that are present in human tumor cells at significantly higher levels than in corresponding normal human cells, Dr. Polakis does not state that how many proteins encoded by the 200 genes are expressed at significantly higher levels than in corresponding normal human cells. Dr. Polakis states that antibodies to about 30 of the tumor antigen proteins have been developed and used to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. Dr. Polakis does not state that the 30 "tumor antigen proteins" are expressed at significantly higher levels in human tumor cells than in corresponding normal human cells. Moreover, the declaration does not provide data such that the Examiner can independently analyze and draw conclusions. Only Dr. Polakis' conclusions are provided in the declaration. There is no evidentiary support to Dr. Polakis' statement that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoding polypeptide. In fact, the art teaches the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (Haynes et al., Electrophoresis, 19:1862-1871, 1998; see, left column of page 1863; Figure 1). While the absolute

certainty is not the legal standard for utility, a specific and substantial utility in reasonably confirmed and practical form is required for the claimed invention.

Appellants, along with the Grimaldi and Polakis declarations, also provide teachings from Molecular Biology of the Cell by Bruce Alberts and Genes VI (1997) by Ben Lewin, to support their assertion that there is a correlation between increased gene expression and increased protein expression (pages: 26-27 of the Brief). Appellants also refer to additional articles by Zhigang et al., and Meric et al. as providing evidence that gene amplification generally results in elevated levels of the encoded polypeptide. Zhigang et al. describe a specific example of the expression of prostrate stem cell antigen (PSCA) protein and mRNA to validate it as potential molecular target for diagnosis and treatment of human prostrate cancer. It is asserted that the data shows " a high degree of correlation between PSCA protein and mRNA expression". Further Meric et al. states "the fundamental principle of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells. Meric et al. also teaches that most efforts have concentrated on identifying differences in gene expression at the level of mRNA, which can be attributable to either DNA amplification or to differences in transcription. Although, Appellants contend that the regulation is primarily at the transcriptional level (based on teachings found in Molecular Biology of the Cell), the prior art references discussed above teach that gene expression is quite complicated and is regulated at the level of mRNA transcription, mRNA stability, mRNA translation and protein stability. In addition, unlike the instant invention, Zhigang et al. provide immunohistochemical analysis and mRNA hybridization to correlate the mRNA

expression with the protein for a known prostate stem cell antigen (PSCA). Unlike the instant PRO1180 polypeptide, PSCA is well characterized and is a cell surface antigen that is predominantly prostrate specific (see page 2). Further reading of Meric et al. seems to teach away from Appellants' claim that there is a direct correlation between increased mRNA levels and the level of expression of the encoded protein. For example, the reference discloses that variations in mRNA sequences increase or decrease translational efficiency as found in BRCA1 (see pages 973-974). In addition, advances in technology, allowing comparisons of message and protein using proteomics, show a lack of correlation, as is evidenced by Haynes et al., Chen et al., and Gygi et al.

Appellants assert that declarations of Grimaldi and Polakis, the accompanying references, and the excerpts and references discussed establish that the accepted understanding in the art is that there is a reasonable correlation between changes in gene expression and changes in the in the level of the encoded protein. It is the contention of the Appellants that substantial amount of evidence supporting their position has been provided and criticizes the Examiner for not providing adequate references to support the lack of utility. Appellant's argument has been fully considered, but is not deemed to be persuasive for the reasons set forth immediately above. Therefore, considered as a whole, the overwhelming amount of evidence it is believed that the rejection should be sustained.

At the p. 28 of the Brief, Appellant argues that the asserted utility for PRO1180 as a cancer diagnostic is specific. The examiner agrees.

Appellants on pages 29-31 of the Brief argue that the Examiners response to 1st Grimaldi declaration is not adequate and remind the Examiner that the declaration of Mr. Grimaldi is based on personal knowledge of the relevant facts at issue. Further it is asserted "[o]ffice personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being question." In addition, it is argued that declarations relating to issues of fact should not be summarily dismissed as "opinions' without adequate explanation of how the declaration fails to rebut the Examiners' position. Appellants maintain that the procedures used to detect differences in expression levels were sufficiently sensitive to detect two-fold differences (see page 30 of the Brief)). Appellant further argue that the Examiner has not supplied any reasons or evidence to question the accuracy of the facts upon which Mr. Grimaldi based his opinions. Contrary to Appellants assertions that the Examiner has not supplied any reason or evidence in support of his position, the Examiner offered evidence from the literature which cautions researchers against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue (see Hu et al., page 5 of the Office Action dated 12/30/2004). In addition and as indicated above, Mr. Grimaldi has an interest in the case, since he is employed by the assignee. Finally, while Mr. Grimaldi bases his findings with reference to facts, the facts are not independently provided for the examiner to draw independent conclusions. For example, it is not clear if any of the tumors were from rectum or kidney etc., or how highly amplified the genes were that correlated with polypeptide overexpression.

Appellants on pages 31-32 of the Brief argue that the Examiners arguments to 2nd Grimaldi declaration fail to establish that one of skill in the art would doubt Appellants' asserted utility. The Examiner in the Office Action mailed 6/14/2005 (page 9) indicated that the PRO1180 gene, unlike Her2/Neu, has *not* been associated with tumor formation or the development of cancer, nor has it been shown to be predictive of such. Similarly, unlike t (5;14), no translocation of PRO1180 gene is known to occur. All that the specification demonstrates is that the PRO1180 nucleic acid (mRNA) was more highly expressed in normal kidney or rectal tumor compared to kidney tumor or normal rectum tissues. No mutation or translocation of PRO1180 has been associated with rectal or kidney cancer. In the absence of any of the above information, all that the specification does is present evidence that the cDNA encoding PRO1180 polypeptide is amplified in an unknown number of samples, and invite the artisan to determine the rest of the story. Contrary to Appellants assertion that the Examiner fails to establish how the "absence of any of the above information" is relevant to the asserted utility by supplying evidence or reasoning to support his assertion, the Examiner indeed has provided the reasoning that PRO1180 gene is not associated with tumor formation and no translocation has been associated with PRO1180 unlike Her2/Neu or t(5;14) discussed above and in the Grimaldi declaration. Even if the differential message expression can be used in the diagnosis of cancer, the lack of a nexus between the differential message expression and polypeptide of PRO1180 or antibodies binding the polypeptide of PRO1180, make the rejections for lack of utility proper. Furthermore, Appellants have cited example 12 from the utility guidelines for consideration (page 32

in the brief). This has been fully considered but the fact patterns are different between example 12 and the instant invention. In example 12, it is stated that the "specification discloses that receptor A is present on the cell membranes of melanoma cells but not on the cell membranes of normal skin cells. However, the instant disclosure does not provide any such disclosure. Appellants also provide several patents in which apparently analogous fact pattern exists. As indicated by the Appellants themselves "... actions taken in other applications are not binding on the PTO with respect to the present application." Appellants also argue that they only relied on paragraph 5 of the declaration for their support. This is not found to be persuasive because the Examiner considered the entire declaration in evaluating its relevance/support to the instant invention.

On page 30 (top) of the Brief Appellants also state that the Examiner has taken out of context Mr. Grimaldi's assertion in the 1st declaration that "additional studies can then be conducted if further information is desired". On the contrary, the Examiner did not take this statement out of context. It was assumed that if there was differential expression of the message that was detected further studies could be conducted to determine nexus to the protein and the antibodies binding such.

From p. 33 to p. 34 of the Brief, Appellant comments upon the examiner's evaluation of the Polakis declaration. Specifically, Appellant argues that the Polakis declaration was submitted to support the position that there is a correlation between mRNA and polypeptide levels. Appellant urges that the opinions in the Polakis declaration are all based on factual findings. Appellant cites case law concerning the

examiner's requirement to consider all of the evidence of record anew, and that opinion evidence must be considered. Appellant also points to the utility guidelines as directing the examiner to accept an opinion from an expert. Appellant points to the statement in the Polakis declaration that it is Dr. Polakis' considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates with a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. Appellant concludes that the fact-based conclusions of Dr. Polakis would be considered reasonable and accurate by the skilled artisan. This has been fully considered but is not found to be persuasive. As discussed above, in assessing the weight to be given expert testimony, the examiner may properly consider, among other things, (1) the nature of the fact sought to be established, (2) the strength of any opposing evidence, (3) the interest of the expert in the outcome of the case, and (4) the presence or absence of factual support for the expert's opinion. In the instant case, the nature of the fact sought to be established (1) is whether or not increased mRNA levels are predictive of increased polypeptide levels. The art provides strong evidence (2) that increased mRNA levels do not correlate with increased protein levels in both healthy and cancerous tissues. See Haynes et al., Gygi et al., Hu et al., and Chen et al. Additionally, Dr. Polakis has an interest in the case since he is employed by the assignee (3). Finally, while Dr. Polakis bases his findings with reference to facts, the facts are not independently provided for the examiner to draw independent conclusions (4). For example, it is not clear if any of the tumors were from kidney or rectum, or how highly amplified the genes were that correlated with polypeptide

overexpression. Based on the totality of the evidence, it is maintained that one skilled in the art would view the instant differential mRNA expression data as merely preliminary with regard to whether or not protein levels of PRO1180 are differentially expressed in kidney or rectal tumors. Further research would have to be done in order to determine if PRO1180 protein are differentially expressed and, if so, whether or not the differential expression is significant enough to reasonably confirm the usefulness of PRO1180 protein as a rectal or kidney cancer marker. Thus, the claimed invention does not provide products or services in "currently available" to the public, and the asserted utility is not substantial. Again, Appellants emphasize that the data in Example 18 are for gene expression, not gene amplification. This has been previously conceded by the Examiner, and does not affect the position of the Examiner in challenging the asserted utility of the instant invention or the Polakis declaration. Further, contrary to Appellants assertion on page 32, the Examiner maintains that there is no nexus between the mRNA levels of the instant invention and polypeptide of PRO1180 or the antibodies binding such.

Appellants on pages 34-35 of the Brief argue that the Examiner has only responded to Meric et al. reference in the Office Action dated 7/06/05. This is not found to be persuasive (see pages 11-13 of the Office Action). Zhigang et al. described a specific example of the expression of prostrate stem cell antigen (PSCA) protein and mRNA to validate it as potential molecular target for diagnosis and treatment of human prostrate cancer. It is asserted that the data shows " a high degree of correlation between PSCA protein and mRNA expression". Further Meric et al. stated that "the

fundamental principle of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells. Meric et al. also teaches that most efforts have concentrated on identifying differences in gene expression at the level of mRNA, which can be attributable to either DNA amplification or to differences in transcription. Although, Appellants contend that the regulation is primarily at the transcriptional level (based on teachings found in Molecular Biology of the Cell), the prior art references discussed above teach that gene expression is quite complicated and is regulated at the level of mRNA transcription, mRNA stability, mRNA translation and protein stability. In addition, unlike the instant invention, Zhigang et al. provide immunohistochemical analysis and mRNA hybridization to correlate the mRNA expression with the protein for a known prostate stem cell antigen (PSCA). Further, unlike the instant PRO1180 polypeptide, PSCA is well characterized and is a cell surface antigen that is predominantly prostrate specific (see page 2). In addition reading of Meric et al. seems to teach away from Appellants' claim that there is a direct correlation between increased mRNA levels and the level of expression of the encoded protein. For example, the reference discloses that variations in mRNA sequences increase or decrease translational efficiency as found in BRCA1 (see pages 973-974). Contrary to Appellants assertion the Examiner did address Hanna et al. in the Office Action dated 7/06/2005. Appellants also assert that in general, FISH and IDC results correlate well (see Page 35 of the Brief). Appellants argues that Hanna et al. disclose that gene amplification and protein overexpression are well correlated, and that only a subset of tumors show discordant results. Appellants argues that Hanna et al. support

Appellant's position that it is more likely than not that gene amplification correlates with increased polypeptide expression. However, Hanna et al. clearly show that the skilled artisan does not assume that any tumor with a HER-2/neu gene amplification event also overexpressed HER-2/neu protein. It is tested empirically. The reason for the testing is irrelevant to the issue at hand. The fact remains that the instant specification does not disclose whether or not PRO1180 protein is overexpressed in any tumors. Therefore, the skilled artisan must perform further research in order to reasonably confirm whether it is or is not. The requirement for such further research indicates that the asserted utility of PRO1180 as a cancer diagnostic agent is not substantial. The specification does not assert that PRO1180 is useful as an agent to categorize tumors. However, even if it had, the specification does not disclose the expression levels of PRO1180 protein in any tumor samples, so that such would have to be determined through further research on the part of the skilled artisan. Thus, even the utility proposed regarding the usefulness of PRO1180 protein in the categorization of tumors, is not substantial. Finally, there is no disclosure regarding what treatment modality should be chosen by the clinician based on whether or not PRO1180 polypeptide is overexpressed. The determination of such constitutes further experimentation, indicating that the asserted utility is not substantial.

Appellants argue extensively in pages 36-42 of the brief that courts have held that the utility requirement was satisfied in similar cases. Finally on page 43 of the Brief, Appellant concludes by stating that the instant specification discloses a specific, credible and substantial utility for the antibodies of PRO1180 polypeptide as a

diagnostic marker for kidney or rectal tumors. The Examiner believes that the rejections should be sustained for the reasons set forth above.

II. Rejection of claims 1-5 under 35 USC § 112, 1st paragraph, enablement

Claims 1-5 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Appellant refers to the arguments and information presented in response to the rejection under 35 U.S.C. § 101 (see page 43 of the brief). Appellant submits that the PRO1180 polypeptides have utility in the diagnosis of cancer. The Examiner believes that the rejection should be sustained for the reasons set forth above.

Therefore, for reasons set forth above, Appellant's arguments and evidence have been fully and carefully considered, but are not considered sufficient to rebut the prima facie case of lack of utility, enablement.

For the above reasons, it is believed that the rejection should be sustained.

III. Rejection of claims 1, 2, and 5 under 35 U.S.C. § 102 (b)

Appellants contend that they are entitled to an earlier priority date that is earlier than that of Edwards et al et al. based on the disclosure of SEQ ID NO: 27 and 28 and the data of Example 18 (differential tissue cDNA expression in tumor versus normal tissue), that was disclosed in PCT Application PCT/US00/23328, filed 8/24/2000 (see

Brief pages 45-46). However, Appellants have not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120. Although, the previous patent application discloses the same polypeptide (SEQ ID NO: 28) sequence and polynucleotides (SEQ ID NO: 27) encoding the polypeptide as the instant specification, the disclosure is not enabling for the instant invention directed to the antibodies binding the polypeptides and because the disclosed function (differential cDNA) expression does not impart utility to the instant invention directed the antibodies binding the polypeptide for the reasons set forth below and the previous Office Actions dated 5/19/04, 12/30/04 and 7/06/05. Therefore, the filing date of 2 May 2002 is maintained as the priority date.

SEQ ID NO: 436 described by Edwards et al has 99.3% identity over first 151 amino acids of SEQ ID NO: 28 of the instant invention (see Office Action of 5/19/04). In addition, Edwards et al. also describe monoclonal antibodies and labelled antibodies (columns 41-42 and 46-47). Therefore, claims 1, 2 and 5 directed to antibodies are anticipated by Edwards et al. (U.S. Patent No: 6,222,029).

IV. Rejection of claims 3 and 4 under 35 U.S.C. § 103 (a)

Claims 3 and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Edwards et al. (U.S. Patent No: 6,222,029) in view of Mack et al. (U.S. Patent No: 6,294,343).

SEQ ID NO: 436 described by Edwards et al has 99.3% identity over first 151 amino acids of SEQ ID NO: 28 of the instant invention (see Appendix A). In addition,

Edwards et al. also describe monoclonal antibodies and labelled antibodies (columns 41-42 and 46-47). However, it does not describe antibody fragments and labelled antibodies. Mack et al. describe humanized and fragments of antibodies (column 22). Therefore, it would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to generate antibodies as taught by Mack et al. using the polypeptide described in Edwards et al that has 99.3% identity to SEQ ID NO: 28 over the first 151 amino acids of the instant invention. The person of ordinary skill in the art would have been motivated to generate antibodies directed to the polypeptide described by Edwards et al. because this will allow the one of skilled in the art use the antibodies to purify the protein or imaging studies or for therapeutic or diagnostic purposes. There is a reasonable expectation of success because Mack et al. have used the antibodies for purification and imaging (columns 24-26). Therefore, the claims are obvious over Edwards et al. (U.S. Patent No: 6,222,029) in view of Mack et al. (U.S. Patent No: 6,294,343).

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted

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